REPORTS ON THERAPY

Randomized, Double-Blind Comparison of Propranolol Alone and a Propranolol-Verapamil Combination in Patients With Severe Angina of Effort

MICHAEL D. WINNIFORD, MD, ROBERT L. HUXLEY, MD, L. DAVID HILLIS, MD, FACC

Dallas, Texas

This study compared propranolol alone with a combination of propranolol and verapamil in patients with severe, limiting angina of effort. Accordingly, 13 men (average age 57 years) with severe angina were enrolled in a study of 7 weeks' duration. Throughout the study, a stable dose of propranolol (295 ± 83 [mean ± standard deviation] mg/day) was administered. In addition to propranolol therapy, each patient was given 2 weeks of up-titration of open label verapamil, 1 week of verapamil down-titration and two 2 week periods of randomized, double-blind therapy, one of placebo and the other of verapamil (431 ± 77 mg/day). A propranolol-verapamil combination caused a decline in anginal episodes/week (7.3 ± 6.9/week during propranolol-placebo, 4.7 ± 5.0/week during propranolol-verapamil, p = 0.03) and nitroglycerin tablets used/week (7.6 ± 6.6/week during propranolol-placebo, 4.4 ± 4.2/week during propranolol-verapamil, p = 0.008). With propranolol-placebo, all 13 patients had angina after 4.6 ± 2.1 minutes of supine bicycle exercise. With propranolol-verapamil, five had no angina with exercise even though their duration of exercise increased; in the other eight, time to angina increased (from 4.0 ± 1.5 minutes with propranolol-placebo to 5.3 ± 1.6 minutes with propranolol-verapamil, p = 0.01).

A propranolol-verapamil combination induced no change in rest or peak exercise left ventricular volumes or ejection fraction (assessed by equilibrium gated blood pool scintigraphy). With propranolol-verapamil, four patients had PR interval prolongation, and two had fatigue and dyspnea. In addition, two had marked sinus bradycardia with junctional escape rhythm that was resolved with a reduction of verapamil dosage. No patient developed congestive heart failure or high degree atrioventricular block. Thus, a combination of propranolol and verapamil is superior to propranolol alone in patients with severe, limiting angina, but such a combination must be used cautiously because of potentially serious adverse effects.

The beta-adrenergic blocking agents, such as propranolol, are highly effective in the treatment of patients with stable angina pectoris (1–9). By reducing myocardial oxygen demand, these drugs reduce anginal frequency and increase exercise tolerance in most patients with angina of effort. However, because some individuals continue to have limiting angina despite substantial amounts of propranolol, they may require additional medical therapy. Several studies (10–14) have demonstrated that verapamil, a calcium antagonist, exerts a salutary effect in patients with angina of effort, and a recent assessment (15) has shown that the combination of propranolol and verapamil prolongs exercise duration in hospitalized patients with severe angina. However, previous studies have not evaluated the efficacy and safety of a propranolol-verapamil combination in a randomized, double-blind study design, nor have they assessed this drug combination in an outpatient setting. The present study compared propranolol alone with a propranolol-verapamil combination in a randomized, double-blind trial involving a group of ambulatory patients with severe, limiting angina despite large doses of propranolol.

From the Department of Internal Medicine (Cardiovascular Division), the University of Texas Health Science Center, Dallas, Texas. This work was supported by Ischemic SCOR Grant HL 17669 from the National Institutes of Health, Bethesda, Maryland, and by the Harry S. Moss Heart Fund, Dallas, Texas. Dr. Hillis is an Established Investigator of the American Heart Association, Dallas, Texas. Manuscript received July 15, 1982; revised manuscript received September 23, 1982; accepted September 29, 1982.

Address for reprints: L. David Hillis, MD, Room L5 134, University of Texas Health Science Center, 5323 Harry Hines Boulevard, Dallas, Texas 75235.

0735-1097/83/020492-7$03.00

J AM COLL CARDIOL
1983;1(2) 492–8

Methods

Study Patients

The study population consisted of 13 men with an average age of 57 years (range 47 to 68). All had severe angina of effort despite a maximal tolerated dose of propranolol (295 ± 83 [mean ± standard deviation] mg/day; range 160 to 480). Selective coronary arteriography revealed significant coronary artery disease (defined as ≥ 70% luminal diameter narrowing) in all patients (triple vessel in 11, double vessel in 1, single vessel in 1); 7 had undergone coronary artery bypass surgery in the remote past. Prior to enrollment, all patients had a positive exercise tolerance test, with angina and at least 1 mm of ST segment depression at peak exercise.

Two of the 13 patients were maintained throughout the study on a stable dose of oral isosorbide dinitrate (150 and 200 mg/day); in these individuals, several attempts to taper or discontinue long-acting nitrates resulted in a marked worsening of angina. One patient was maintained on digoxin and quinidine therapy for the control of supraventricular tachyarrhythmias. With these exceptions, no other cardiac medications were administered during the study.

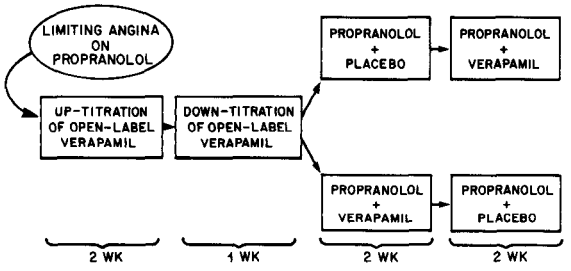
Patients with any of the following were excluded from the study: congestive heart failure; uncontrolled systemic arterial hypertension; hypotension; associated valvular or congenital cardiac disease; renal or hepatic disease; any terminal illness; certain electrocardiographic abnormalities, including severe bradycardia, atrioventricular block of any degree, or atrial flutter or fibrillation; or concomitant therapy with disopyramide or another investigational agent.

Study Design (Fig. 1)

All 13 patients entered the study receiving large doses of propranolol; this dosage was administered during the entire 7 week study. After informed consent was obtained, each was begun on treatment with open label verapamil. During a 2 week up-titration period, the maximal dose of verapamil that did not cause adverse effects was determined. Specifically, each patient was initially given 120 mg/day (40 mg, 3 times daily) of verapamil for 3 days, at which time he was seen by one of the investigators, and a 12 lead electrocardiogram was performed. Subsequently, at 3 day intervals, the dose of verapamil was increased to 160, 240, 320 and 480 mg/day. With each increase in verapamil dosage, the patient was interviewed and examined, and a 12 lead electrocardiogram was recorded. In this manner, the maximal tolerated dosage of verapamil was determined for each patient and was employed during the blinded portion of the study.

After a 1 week period of down-titration of verapamil, each patient was randomly assigned to one of two groups for the remaining 4 weeks of the study (Fig. 1): two 2 week periods of a propranolol-placebo combination and a propranolol-verapamil combination. During this period, placebo and verapamil were administered in a double-blind fashion, so that neither the physicians nor the patients knew which agent was being given. In short, these 4 weeks of randomized, double-blind therapy allowed a direct comparison of the maximal tolerated dose of propranolol alone and the maximal tolerated doses of propranolol and verapamil in combination.

Figure 1. Schematic outline of the study design. All patients entered the study with severe, limiting angina despite propranolol therapy. After a 2 week up-titration and a 1 week down-titration period of open label verapamil, each patient was randomly assigned to one of two groups for the remaining 4 weeks of the study. 2 weeks of propranolol-placebo, 2 weeks of propranolol-verapamil. These 4 weeks of combination therapy were double-blind.



Variables Analyzed

Clinical response to therapy. Each of the patients was seen weekly by one of the investigators, and the following were quantitated: (1) episodes of angina per week (recorded daily by the patient in a diary), (2) nitroglycerin tablets used per week (assessed by tablet counts), and (3) adverse effects (recorded by the patient in a diary). During both periods of blinded therapy, ambulatory electrocardiographic (Holter) monitoring was performed for 24 hours, and the tapes were analyzed for arrhythmias and conduction disturbances.

Exercise tolerance testing. Near the end of both 2 week periods of blinded therapy, maximal supine bicycle exercise testing with simultaneous equilibrium gated blood pool scintigraphy was performed 90 to 120 minutes after a regularly scheduled dose of propranolol and study medication. Rest and exercise electrocardiograms were monitored with a truncal 12 lead system. Exercise was commenced at 150 kilipond-meters (kp-m) per minute and increased incrementally by 150 kp-m every 4 minutes until one of the following occurred: (1) exhaustion, (2) angina of at least moderate severity, or (3) frequent ventricular ectopy. From each exercise test, the following were quantitated: (1) the *clinical* response to exercise, as reflected by the time to onset of angina and the total duration of exercise; (2) the *hemodynamic* response to exercise, as assessed by the heart rate and heart rate-systolic arterial pressure (rate-pressure) product both at rest and during exercise; (3) the *electrocardiographic* response to exercise, as assessed by the magnitude of ST segment depression at peak exercise in comparison with that at rest; and (4) the *scintigraphic* response to exercise, as reflected by left ventricular end-diastolic and end-systolic volumes and ejection fraction at rest and during exercise, as previously described (14,16–22).

Data Analysis

All patient diaries, nitroglycerin tablet counts, Holter monitor recordings and exercise tolerance tests were analyzed without knowledge of the order in which placebo and verapamil were administered. The clinical characteristics of the patients initially assigned to placebo were compared with those of the patients initially assigned to verapamil: there were no differences, confirming that the initial assignment was random. For each variable,

a paired *t* test and Wilcoxon matched pairs signed ranks test were used to compare propranolol-placebo therapy with propranolol-verapamil therapy. In comparing rest and peak exercise values during treatment with the same pharmacologic agent, the paired *t* test was used. For all analyses, a probability (p) value of 0.05 or less was considered significant (23,24).

Results

Drug Compliance and Dosage

Compliance (assessed by actual tablet counts) averaged 97% (range 82 to 100%) during propranolol-placebo therapy and 96% (range 75 to 100%) (difference not significant [NS]) during propranolol-verapamil therapy. The 13 patients received a mean (± standard deviation) of 431 ± 77 (range 320 to 480) mg/day of verapamil. In each patient, serum concentrations of propranolol and verapamil were measured 90 to 120 minutes after a regularly scheduled dose of study medication. For the 13 patients, the serum propranolol level averaged 87 ± 66 (range 14 to 220) ng/ml, the serum verapamil concentration 171 ± 114 (range 22 to 501) ng/ml, and the serum norverapamil concentration 171 ± 63 (range 40 to 288) ng/ml.

Clinical Response to Therapy

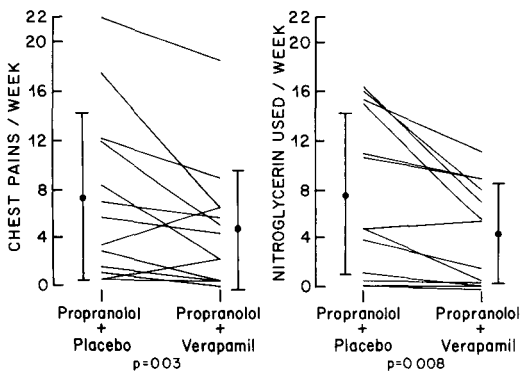
During treatment with propranolol-placebo, the 13 patients had an average of 7.3 ± 6.9 episodes of angina/week and used 7.6 ± 6.6 nitroglycerin tablets/week. During propranolol-verapamil therapy, anginal frequency decreased to 4.7 ± 5.0 episodes/week (p = 0.03) and nitroglycerin usage to 4.4 ± 4.2 tablets/week (p = 0.008) (Fig. 2).

During propranolol-placebo therapy, two patients complained of fatigue. During verapamil administration (open label or blinded), six patients noted adverse effects: four had constipation, two had fatigue and dyspnea and one had palpitation and weakness (coincident with a marked sinus bradycardia and a junctional escape rhythm at 40/min on Holter monitor). During propranolol-verapamil therapy, four patients had asymptomatic prolongation of the PR interval from ≤0.20 to >0.20 second (range 0.21 to 0.26 second). No patient developed second or third degree heart block or objective evidence of left ventricular failure.

One of the 13 patients had substantially depressed left ventricular systolic function. This 59 year old man with severe three vessel coronary artery disease and previous coronary bypass surgery had a left ventricular ejection fraction during propranolol-placebo therapy (320 mg/day) of 0.27 at rest and 0.31 with exercise. During this treatment period, he averaged 22 episodes of angina/week and used 11 nitroglycerin tablets/week. With propranolol-verapamil (320 mg/day of each), his anginal frequency and nitroglycerin usage decreased slightly (18.5 and 9/week, respectively). His left ventricular ejection fraction was 0.25 at rest and 0.21 with exercise. This patient experienced no adverse effects during the study.

One serious adverse effect occurred during the study. An increase in verapamil dosage from 320 to 480 mg/day during the open label up-titration period caused one patient to be hospitalized for angina coincident with a junctional rhythm at a rate of 35 beats/min. There was no evidence of myocardial infarction, and sinus rhythm returned after the verapamil dose was reduced to 320 mg/day. Subsequently, this patient completed the study without further adverse reactions.

Figure 2. Number of episodes of chest pain/week (**left**) and the number of nitroglycerin tablets used/week (**right**) during propranolol-placebo and propranolol-verapamil therapy. Each line represents the data from one patient, and the means ± 1 standard deviation are displayed on either side of each set of lines. During propranolol-verapamil therapy, the number of episodes of chest pain and nitroglycerin tablets consumed was lower than during propranolol-placebo therapy.



Exercise Tolerance Testing

Symptomatic response to exercise. During propranolol-placebo therapy, all 13 patients developed angina after an average of 4.6 ± 2.1 (range 2 to 10) minutes of exercise. With propranolol-verapamil, five patients exercised to fatigue without angina, even though exercise duration for these five increased from 7.4 ± 3.1 minutes with propranolol-placebo to 10.3 ± 3.1 minutes with propranolol-verapamil ($p < 0.01$). In the remaining eight patients, exercise time to angina increased from 4.0 ± 1.5 minutes on propranolol-placebo to 5.3 ± 1.6 minutes on propranolol-verapamil (p = 0.01). For all 13 patients, the total exercise duration was 6.8 ± 2.4 minutes on propranolol-placebo and 8.2 ± 2.9 minutes on propranolol-verapamil ($p < 0.05$) (Table 1).

Hemodynamic response to exercise (Fig. 3). The addition of verapamil to propranolol did not cause a significant change in rest heart rate, systolic arterial pressure or rate-pressure product (Table 1, Fig. 3). At peak exercise, heart rate was lower (p = 0.03) during propranolol-verapamil than during propranolol-placebo therapy (Fig. 3). Systolic arterial pressure at peak exercise was similar during both treatment periods. Because of the lower heart rate at peak

J AM COLL CARDIOL
1983;1(2) 492–8

Table 1. Clinical, Hemodynamic and Scintigraphic Variables During Exercise Tolerance Testing

Variable	Propranolol + Placebo	Propranolol + Verapamil
Clinical		
Exercise duration (minutes)	6.8 ± 2.4	8 2 ± 2.9*
Hemodynamic		
Heart rate (beats/min)		
At rest	57 ± 5	56 ± 6
At peak exercise	82 ± 8	76 ± 9*
Systolic blood pressure (mm Hg)		
At rest	136 ± 25	130 ± 20
At peak exercise	159 ± 31	151 ± 23
Heart rate-systolic arterial pressure product ($\times 10^3$)		
At rest	7 7 ± 1 7	7 3 ± 1.8
At peak exercise	13.0 ± 2.9	11.6 ± 2.6*
Scintigraphic		
LVEDVI (ml/m^2)		
At rest	78 ± 15	81 ± 16
At peak exercise	82 ± 19	86 ± 17
LVESVI (ml/m^2)		
At rest	36 ± 18	37 ± 12
At peak exercise	42 ± 20	40 ± 15
LVEF		
At rest	0.58 ± 0 12	0.57 ± 0.13
At peak exercise	0 55 ± 0.12	0 56 ± 0.15

Values are expressed as mean values ± standard deviation
*$p < 0$ 05 in comparison with propranolol + placebo
LVEDVI = left ventricular end-diastolic volume index, LVEF = left ventricular ejection fraction, LVESVI = left ventricular end-systolic volume index

exercise during propranolol-verapamil therapy, the rate-pressure product at peak exercise was lower during such combination therapy (Table 1, Fig. 3).

Electrocardiographic response to exercise. During therapy with propranolol-placebo, the 13 patients had 0.13 ± 0.09 mV of ST segment depression at peak exercise. During propranolol-verapamil therapy, these patients had only 0.08 ± 0.08 mV of ST segment depression ($p = 0.007$), even though (as mentioned previously) exercise duration increased during combination therapy.

Scintigraphic response to exercise (Fig. 4). At rest and peak exercise, left-ventricular end-diastolic volume index, end-systolic volume index and ejection fraction were similar during the propranolol-placebo and propranolol-verapamil treatment periods (Table 1, Fig. 4).

Discussion

Over the past two decades, propranolol has proved highly effective in the therapy of patients with angina of effort (1–9), and verapamil has been shown to be similarly beneficial in patients with this syndrome (10–14). Because both drugs

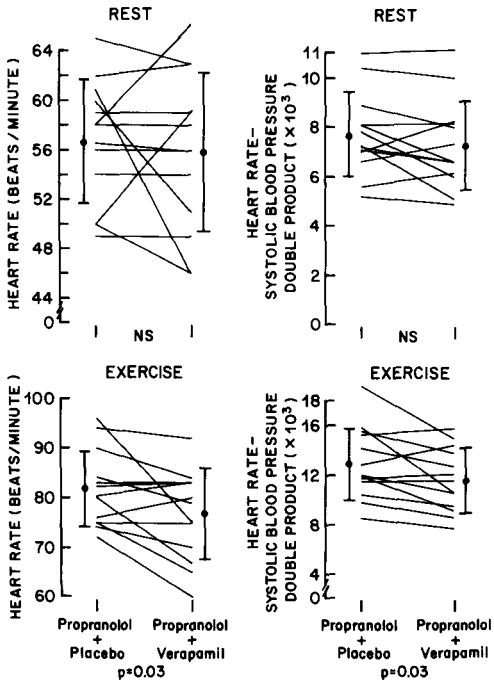
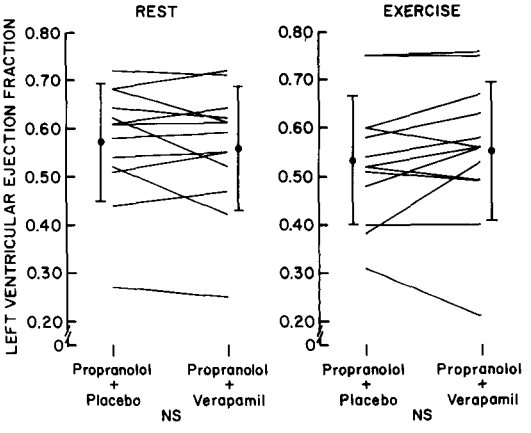


Figure 3. Heart rate at rest (**top left**) and at peak exercise (**bottom left**), as well as heart rate-systolic blood pressure product at rest (**top right**) and at peak exercise (**bottom right**) during each of the two treatment periods. Each line represents the data from one patient, and the means ± 1 standard deviation are displayed on either side of each set of lines. At rest, heart rate and rate-pressure product were similar during both treatment periods. With exercise, propranolol-verapamil reduced both variables.

exert a salutary effect in patients with angina of effort, their combined administration may be especially effective in patients whose angina is limiting despite administration of large doses of only one agent. Indeed, the present randomized and double-blind assessment demonstrates that a propranolol-verapamil combination is superior to propranolol alone in patients with severe angina.

Figure 4. Left ventricular ejection fraction at rest (**left**) and at peak exercise (**right**) during the two treatment periods. Each line represents the data from one patient, and the means ± 1 standard deviation are displayed on either side of each set of lines. The combination of propranolol and verapamil exerted no effect on either rest or peak exercise ejection fraction.



Antianginal mechanisms of propranolol and verapamil. Propranolol exerts antianginal effects in several ways. Most importantly, it diminishes myocardial oxygen demands by reducing the three major determinants of myocardial oxygen consumption—heart rate, systemic arterial pressure and left ventricular contractility (25–27). In addition, propranolol may inhibit enhanced platelet aggregation (28) and may increase tissue oxygen delivery by altering the affinity of hemoglobin for oxygen (29). It does not induce coronary artery dilation and, therefore, does not exert a salutary effect on coronary blood flow. In fact, in patients in whom coronary artery spasm is of etiologic importance, propranolol may actually cause coronary artery vasoconstriction (30). The beneficial effect of verapamil in patients with angina of effort is accomplished first by a reduction in myocardial oxygen requirements. Similar to propranolol, this agent diminishes heart rate, systemic arterial pressure and left venticular contractility (31,32). Second, in contrast to propranolol, verapamil reduces coronary vascular resistance and, as a result, may augment both anterograde (33) and retrograde (34) coronary blood flow.

Because propranolol and verapamil differ somewhat in their antianginal mechanisms, their combined administration may exert an especially beneficial effect. For example, the increase in sympathetic tone occurring in response to verapamil-induced peripheral vasodilation may be blunted by propranolol, thus allowing a marked reduction in left ventricular contractility and myocardial oxygen demand. Alternatively, the propensity of propranolol to increase coronary vascular resistance in patients in whom coronary artery spasm is operative (30) is effectively countered by the direct vasodilating influence of verapamil. Finally, it is conceivable that a propranolol-verapamil combination is especially salutary in patients with angina because one of the two agents in some way induces a pharmacokinetic potentiation of the other. Whatever the exact mechanism(s), a propranolol-verapamil combination may exert a more powerful antianginal effect than either agent alone.

In the present study, the combined administration of propranolol and verapamil did not alter rest heart rate or heart rate-systolic arterial pressure product in comparison with propranolol therapy alone. However, at peak exercise, the drug combination lowered both variables (Fig. 3), reflecting a further reduction in myocardial oxygen requirements. It is unknown whether such combination therapy exerted any effect on myocardial oxygen supply.

Beneficial effects of a propranolol-verapamil combination. In a single-blind assessment of 11 hospitalized patients with severe angina pectoris, Leon et al. (15) showed that a propranolol-verapamil combination was more effective than either agent alone in increasing exercise time and in either delaying or ablating the occurrence of exercise-induced angina. Similar results subsequently have been reported by Subramanian et al. (35). The present randomized, double-blind study of 13 ambulatory outpatients with severe, limiting angina shows that a propranolol-verapamil combination is superior to propranolol alone. Such combination therapy reduced the frequency of angina and the usage of sublingual nitroglycerin (Fig. 2). It increased both exercise duration and the time from onset of exercise to appearance of chest pain, and in five patients, it totally alleviated exercise-induced angina. Left ventricular volumes and ejection fraction, measured both at rest and during supine bicycle exercise, were not affected detrimentally by the propranolol-verapamil combination (Fig. 4). In short, a propranolol-verapamil combination was more effective than propranolol alone in diminishing symptoms and increasing exercise capability.

Adverse effects of a propranolol-verapamil combination. The combination of propranolol and verapamil may produce serious adverse effects, and anecdotal reports (36–39) have described cardiovascular catastrophes when intravenous verapamil was administered to patients already receiving propranolol. Because both agents exert negative inotropic and chronotropic effects, their combined usage may induce left ventricular failure, marked bradycardia or atrioventricular block. In addition, several recent investigations (40–43) have demonstrated that the acute administration of verapamil to patients already receiving propranolol induces no change or deterioration in cardiac output, left ventricular ejection fraction, intracardiac filling pressures and atrio-His conduction. Of the 11 patients reported by Leon et al. (15), combined propranolol-verapamil therapy caused PR interval prolongation in most, transient Wenckebach block in 1 and dyspnea, orthostatic dizziness and pedal edema in 3.

In the present study, no patient developed symptoms or signs of left ventricular failure during combination therapy, and multigated blood pool scintigraphy demonstrated no deterioration of left ventricular systolic performance (Table 1, Fig. 4). Although four patients developed first degree atrioventricular block, none had second or third degree block. Two patients had episodes of marked sinus bradycardia with junctional escape rhythm, one of which was associated with prolonged angina. Although the incidence of adverse effects was small in this study, it should be emphasized that patients with congestive heart failure or conduction system disease were excluded from enrollment and that the uptitration of verapamil was performed slowly and carefully, thus minimizing the chance that combination therapy would cause serious adverse effects. Therefore, propranolol and verapamil should be administered concomitantly with great caution.

Advantages and limitations of the present study. There are several strengths to the present study. First, it is a randomized and double-blind comparison of propranolol alone and a propranolol-verapamil combination. Second, because the 13 study patients had severe, limiting angina despite

maximal tolerated dosages of propranolol, they closely resemble those in whom combination therapy is most seriously considered. Third, the entire study was performed in a group of ambulatory outpatients in whom hospitalization was not employed, even for the verapamil up-titration period. Fourth, in each patient, the maximal tolerated dosage of propranolol was compared with the maximal tolerated dosage of both propranolol and verapamil; that is, the study was designed to compare maximal tolerated—rather than fixed—dosages of each agent.

The present study also has certain limitations. Thirteen patients is not a large number, and, therefore, our results will require confirmation in a greater number of patients. All 13 patients were male; women will probably respond similarly when given a propranolol-verapamil combination, but this, too, will require confirmation. Although the present study demonstrates that a propranolol-verapamil combination is superior to propranolol alone, it does not compare either therapy with verapamil alone. Because Frishman et al. (44) have suggested that verapamil is superior to propranolol, it is conceivable that the efficacy of combination propranolol-verapamil therapy may be similar to that of verapamil alone. Finally, because each blinded treatment period lasted only 14 days, the long-term efficacy and safety of combined propranolol-verapamil therapy cannot be assessed from these data.

Conclusions. In patients with severe, limiting angina despite large doses of propranolol, a propranolol-verapamil combination is effective in relieving angina, reducing nitroglycerin usage and increasing exercise capability. When such combination therapy is administered carefully, it appears reasonably safe, although an occasional patient may develop symptomatic bradycardia or heart block.

We acknowledge the assistance of Kay Lancaster and R. Scott Lyons in the performance of the studies and of Juanita Alexander in the preparation of the manuscript. The support of Knoll Pharmaceutical Company and Searle Laboratories is also appreciated

References

1. Srivastava SC, Dewar HA, Newell DJ Double-blind trial of propranolol (Inderal) in angina of effort Br Med J 1964;2 724–5.
2. Keelan P. Double-blind trial of propranolol (Inderal) in angina pectoris. Br Med J 1965;1:897–8.
3. Nestal PJ. Evaluation of propranolol in the treatment of angina pectoris. Med J Aust 1966;2:1274–6.
4. Grant RHE, Keelan P, Kernohan RJ, Leonard JC, Nancekievill L, Sinclair K. Multicenter trial of propranolol in angina pectoris Am J Cardiol 1966;18:361–5.
5. Wolfson S, Heinle RA, Herman MV, Kemp HG, Sullivan JM, Gorlin R. Propranolol and angina pectoris. Am J Cardiol 1966,18:345–53.
6. Zeft HJ, Patterson S, Orgain ES. The effect of propranolol in the long-term treatment of angina pectoris. Arch Intern Med 1969;124.578–83.
7. Amsterdam EA, Gorlin R, Wolfson S Evaluation of long-term use of propranolol in angina pectoris. JAMA 1969,210.103–6.
8. Mizgala HF, Khan AS, Davies RO. Propranolol in the prophylactic treatment of angina pectoris. Can Med Assoc J 1969;100:756–64.
9. Warren SG, Brewer DL, Orgain ES. Long-term propranolol therapy for angina pectoris. Am J Cardiol 1976;37:420–6.
10. Neumann M, Luisada AA. Double blind evaluation of orally administered iproveratril in patients with angina pectoris. Am J Med Sci 1966;251:552–6.
11. Krikler DM. Verapamil in cardiology. Eur J Cardiol 1974;2:3–10.
12. Andreasen F, Boye E, Christoffersen E, et al. Assessment of verapamil in the treatment of angina pectoris. Eur J Cardiol 1975;2.443–52.
13. Singh BN. Verapamil and the heart. pharmacological and therapeutic considerations. NZ Med J 1975;82:339–43.
14. Johnson SM, Mauritson DR, Corbett JR, Woodward W, Willerson JT, Hillis LD. Double-blind, randomized, placebo-controlled comparison of propranolol and verapamil in the treatment of patients with stable angina pectoris. Am J Med 1981;71:443–51
15. Leon MB, Rosing DR, Bonow RO, Lipson LC, Epstein SE. Clinical efficacy of verapamil alone and combined with propranolol in treating patients with chronic stable angina pectoris. Am J Cardiol 1981;48:131–9.
16 Stokely EM, Parkey RW, Bonte FJ, Graham KD, Stone MJ, Willerson JT. Gated blood pool imaging following technetium-99m pyrophosphate scintigraphy. Radiology 1976;120:433–4.
17. Firth BG, Dehmer GJ, Corbett JR, Lewis SE, Parkey RW, Willerson JT. Effect of chronic oral digoxin therapy on ventricular function at rest and peak exercise in patients with ischemic heart disease Am J Cardiol 1980;46:481–90.
18. Dehmer GJ, Falkoff M, Lewis SE, Hillis LD, Parkey RW, Willerson JT. Effect of oral propranolol on rest and exercise left ventricular ejection fraction, volumes, and segmental wall motion in patients with angina pectoris. Assessment with equilibrium gated blood pool imaging. Br Heart J 1981;45:656–66.
19. Dehmer GJ, Lewis SE, Hillis LD, Corbett J, Parkey RW, Willerson JT. Exercise-induced alterations in left ventricular volumes and the pressure/volume relationship. A sensitive indicator of left ventricular dysfunction in patients with coronary artery disease. Circulation 1981;63:1008–18.
20. Dehmer GJ, Lewis SE, Hillis LD, et al. Determination of left ventricular volumes from the time-activity data derived from equilibrium gated blood pool scans. Am J Cardiol 1980;45:293–300.
21. Ashburn WL, Schelbert HR, Verba J. Left ventricular ejection fraction—a review of several radionuclide angiographic approaches using the scintillation camera. Prog Cardiovasc Dis 1978;20:267–77.
22 Slutsky R, Karliner J, Ricci D, et al. Left ventricular volumes by gated equilibrium radionuclide angiography: a new method. Circulation 1979;60:556–64.
23. Noether GE. Introduction to Statistics. Boston:Houghton Mifflin, 1971:147–9
24. Zar JH. Biostatistical Analysis Englewood Cliffs, NJ: Prentice-Hall, 1974;152–4.
25. Epstein SE, Braunwald E. Beta-adrenergic receptor blocking drugs. Mechanisms of action and clinical applications. N Engl J Med 1966,275:1106–12.
26. Parker JO, West RO, DiGiorgi S. Hemodynamic effects of propranolol in coronary heart disease. Am J Cardiol 1968;21:11–9.
27. Wolfson S, Gorlin R. Cardiovascular pharmacology of propranolol in man Circulation 1969;40:501–11.
28. Frishman WH, Weksler B, Christodonlou JP, Smithen C, Killip T. Reversal of abnormal platelet aggregability and change in exercise tolerance of patients with angina pectoris following oral propranolol Circulation 1974;50·887–96.
29. Schrumpf JD, Sheps DS, Wolfson S, Aronson AL, Cohen LS. Altered hemoglobin-oxygen affinity with long-term propranolol therapy in patients with coronary artery disease. Am J Cardiol 1977.40.76–82.

30. Robertson RM, Wood AJJ, Vaughn WK, Robertson D. Exacerbation of vasotonic angina pectoris by propranolol. Circulation 1982;65:281–5.

31. Nayler WG, Szeto J. Effect of verapamil on contractility, oxygen utilization, and calcium exchangeability in mammalian heart muscle. Cardiovasc Res 1972;6:120–8

32. Roy PR, Spurrell RA, Sowton E. The effect of verapamil on the cardiac conduction system in man. Postgrad Med J 1974;50:270–5.

33. Ono H, Hashimoto K. Calcium antagonism in various parameters of cardiac function including coronary dilatation with the use of nifedipine, perhexiline, and verapamil. In: Ischemic Myocardium and Antianginal Drugs. New York: Raven Press, 1979:77.

34. DaLuz PL, DeBarros L, Leite JJ, Pileggi F, Decourt LV. Effect of verapamil on regional coronary and myocardial perfusion during acute coronary occlusion. Am J Cardiol 1980;45:269–75.

35. Subramanian B, Bowles MJ, Davies AB, Raftery EB. Combined therapy with verapamil and propranolol in chronic stable angina. Am J Cardiol 1982;49:125–32.

36. Benaim ME. Asystole after verapamil. Br Med J 1972;2:169.

37. Boothby CB, Garrard CS, Pickering D. Verapamil in cardiac arrhythmias. Br Med J 1972;2:349.

38. Krikler DM, Spurrell RAJ. Verapamil in the treatment of paroxysmal supraventricular tachycardia. Postgrad Med J 1974;50:447–53.

39. Bassan M, Weiler-Ravell D, Shalev O. Additive antianginal effect of verapamil in patients receiving propranolol. Br Med J 1982,284.1067–70.

40. Kieval J, Kirsten EB, Kessler KM, Mallon SM, Myerburg RJ The effects of intravenous verapamil on hemodynamic status of patients with coronary artery disease receiving propranolol. Circulation 1982;65:653–9.

41. Packer M, Meller J, Medina N, et al. Hemodynamic consequences of combined beta-adrenergic and slow calcium channel blockade in man. Circulation 1982;65:660–8.

42. Bonow RO, Leon MB, Rosing DR, et al. Effects of verapamil and propranolol on left ventricular systolic function and diastolic filling in patients with coronary artery disease: radionuclide angiographic studies at rest and during exercise. Circulation 1982;65:1337–50.

43. Winniford MD, Markham RV Jr, Firth BG, Nicod P, Hillis LD. Hemodynamic and electrophysiologic effects of verapamil and nifedipine in patients on propranolol therapy. Am J Cardiol 1982;50:704–10.

44. Frishman WH, Klein NA, Strom JA, et al. Superiority of verapamil to propranolol in stable angina pectoris: a double-blind, randomized, crossover trial. Circulation 1982;65(suppl I):I-51–9.